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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/601,242	06/20/2003	Phillip Dan Cook	ISIS-5213	6684
32650 7590 01/07/2008 WOODCOCK WASHBURN LLP CIRA CENTRE, 12TH FLOOR 2929 ARCH STREET PHILADELPHIA, PA 19104-2891			EXAMINER EPPS FORD, JANET L	
			ART UNIT 1633	PAPER NUMBER
			MAIL DATE 01/07/2008	DELIVERY MODE PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<p align="center"><b>Advisory Action</b> <b>Before the Filing of an Appeal Brief</b></p>	<p><b>Application No.</b> 10/601,242</p>	<p><b>Applicant(s)</b> COOK ET AL.</p>	
	<p><b>Examiner</b> Janet L. Epps-Ford</p>	<p><b>Art Unit</b> 1633</p>	

**--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

THE REPLY FILED 19 December 2007 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

- a) ☒ The period for reply expires 4 months from the mailing date of the final rejection.  
b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**NOTICE OF APPEAL**

2. ☐ The Notice of Appeal was filed on \_\_\_\_\_. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

**AMENDMENTS**

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because  
(a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);  
(b) ☐ They raise the issue of new matter (see NOTE below);  
(c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or  
(d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: \_\_\_\_\_. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).  
5. ☒ Applicant's reply has overcome the following rejection(s): See Continuation Sheet.  
6. ☐ Newly proposed or amended claim(s) \_\_\_\_\_ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).  
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.  
The status of the claim(s) is (or will be) as follows:  
Claim(s) allowed: \_\_\_\_\_.  
Claim(s) objected to: \_\_\_\_\_.  
Claim(s) rejected: 44 and 69-73.  
Claim(s) withdrawn from consideration: \_\_\_\_\_.

**AFFIDAVIT OR OTHER EVIDENCE**

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).  
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing of good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).  
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

**REQUEST FOR RECONSIDERATION/OTHER**

11. ☐ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: \_\_\_\_\_  
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). \_\_\_\_\_  
13. ☒ Other: see attached.

/Janet L. Epps-Ford/  
Primary Examiner  
Art Unit: 1633

Continuation of 5. Applicant's reply has overcome the following rejection(s): The rejection of claims 72-73 as unpatentable over Uhlmann et al., Cook et al., Secrist et al., and Sorge et al.

### DETAILED ACTION

1. Claims 44, and 69-73 are pending for examination.
2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

### *Response to Arguments*

#### ***Claim Rejections - 35 USC § 103***

3. Claims 44, and 69-71 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Uhlmann et al., Cook et al., Secrist et al., and Sorge et al. for the reasons of record.
4. Applicant's arguments filed 12-19-2007 have been fully considered but they are not fully persuasive. The examiner agrees with Applicant that the citation of Secrist et al., other than its disclosure of the synthesis of 2'-deoxy-4'-thio pyrimidines nucleosides, does not suggest the incorporation of this compound into the oligonucleotides of the invention. Moreover, the examiner agrees that Sorge et al. also does not suggest the incorporation of 4'thionucleosides into the compounds of the invention. However, the examiner *does not* agree that due to the extensive disclosure of both the Uhlmann et al. and Cook et al. references that the claimed invention, at least to the extent that it reads on a compound *comprising* a first region including a plurality of  $\alpha$ -nucleosides and a second region including at least 5 consecutive 2'-deoxy-erythro-pentofuranosyl  $\beta$ -nucleosides, is non-obvious over the prior art.
5. Although Applicants argue that because the disclosure of Uhlmann et al. mentions 18 different modifications, the ordinary skilled artisan would have not been

motivated to modify oligonucleotides to comprise alpha-nucleosides. Contrary to Applicant's assertions, despite the breadth of the Uhlmann et al. reference it is clear that the benefits of introducing alpha-nucleosides into oligonucleotides was known prior to the filing of Applicant's invention as now claimed.

6. Moreover, as stated in the prior Office Action Cook et al. teach the following compound on page 163, line 33: 5'-Gaa-GTC-aCT-GgaaCG-3', wherein **a** is a 2'-deoxy- $\alpha$ -D-adenosine nucleoside. This compound comprises a region of  $\alpha$ -nucleosides and a region of  $\beta$ -deoxynucleosides synthesized by solid phase DNA synthesis from 5'-DMT-3'- $\beta$ -cyanoethyl-diisopropyl-phosphoramidite protected deoxynucleosides. This compound comprises two regions, a region comprising  $\alpha$ -nucleosides, and a region comprising 2'-deoxyerythropentofuranosyl- $\beta$ -nucleosides. Moreover, at page 4, last two paragraphs, it is clear that oligonucleotides comprising alpha-nucleosides and those comprising deoxy type nucleosides both function as antisense agents.

7. The only difference in the instant case is the number of 2'-deoxyerythropentofuranosyl- $\beta$ -nucleosides in the compound recited in Cook et al. and the presence of a "plurality of consecutively linked" alpha-nucleosides in the molecule. *Absent evidence to the contrary*, it would have been obvious to the ordinary skilled artisan seeking alternative antisense compounds, would have been motivated to vary the number of alpha-nucleosides and 2'-deoxyerythropentofuranosyl- $\beta$ -nucleosides in the oligonucleotide to produce a similar compound, having the same properties as the prior art compound, namely for use as an antisense agent. One of ordinary skill in the art would have recognized the benefits of introducing alpha nucleosides into

oligonucleotides as taught by Uhlmann et al., and would have been motivated to introduce this class of modification into an antisense oligonucleotide, with the expectation that the modification would confer enhanced stability toward nucleases.

8. Applicants traverse the instant rejection on the grounds that the proposed combination impermissibly exploits the hindsight provided by Applicant's own disclosure. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

***Claim Rejections - 35 USC § 112***

9. Claims 44 and 69-73 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. (New Matter).

10. Applicant's arguments filed 12-19-07 have been fully considered but they are not persuasive. Applicants traversed the instant rejection on the grounds that the patent laws do not require verbatim support and those skilled in the art reading the instant

specification would readily understand that Applicants were in possession of the claimed subject matter. The examiner agrees that the specification as filed provides as filed discloses an oligonucleotide comprising a 4 nucleotide long region of  $\alpha$ -nucleotides (see Example 2A), and an oligonucleotide comprising a region of four 4'-thionucleotides (Example 7). Moreover, the examiner recognizes support in the disclosure for oligonucleotides that *may include a plurality of consecutive* 4'-thionucleosides or  $\alpha$ -nucleosides. However, this disclosure is not sufficient to provide support for the instantly claimed invention that specifically recites a first region comprising a plurality of consecutively 4'-thionucleosides or  $\alpha$ -nucleosides, linked by charged 3'-5' phosphorous linkages, **and** a second region comprising at least 5 consecutive 2'-deoxy-erythro-pentofuranosyl  $\beta$ -nucleosides linked by charged 3'-5' phosphorous linkages.

11. See MPEP § 2163.05 [R-2].II., citing *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996), states "[a] 'laundry list' disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not 'reasonably lead' those skilled in the art to any particular species." In the instant case, Applicant's disclosure recites a laundry list of possible modifications to an oligonucleotide. There is no support either implicit or explicit in the specification that would lead the skilled artisan to select an oligonucleotide comprising an undefined number of 4'-thionucleosides or  $\alpha$ -nucleosides, and further to comprise a region comprising at least 5 consecutive 2'-deoxy-erythro-pentofuranosyl  $\beta$ -nucleosides.

It remains that Applicant's amendment is therefore considered new matter.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford whose telephone number is 571-272-0757. The examiner can normally be reached on M-F, 10:00 AM through 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Janet L. Epps-Ford/  
Primary Examiner  
Art Unit 1633

JLE